Lesson 03: the tablet dosage form

1. **Definition:**

A tablet is a solid pharmaceutical form containing a single dose of an active substance, obtained by compressing powder or granules. It is intended to be swallowed, chewed, or dissolved in water, and may be coated to modify its appearance or release.

• Components: Tablets are composed of the active substance, along with excipients such as diluents, binders, disintegrants, or lubricants, which help make the tablet and control its release.

• Administration: They are primarily designed for oral administration, but variations exist for other uses, such as lozenges, sublingual tablets, or dispersible tablets.

• Purpose: The tablet shape is designed to allow for absorption of the active substance by the body, ensuring that it disintegrates properly in the stomach to facilitate dissolution.

• Characteristics: They are generally cylindrical in shape, but can be breakable (with a break bar), coated, or bearing inscriptions

2. Adjuvants

These are chemically and physiologically inert mineral or organic powders used in tablet formulation. These excipients or adjuvants can be classified into several categories depending on their role in the formulation. The main categories are:

a. **Diluents**. These are bulking agents considered "inert" and are added to achieve the desired tablet size. Typically, in the case of low-dose products where the amount of active ingredient is too small, they are added to increase the weight so that the tablet form can be prepared. Examples are sugars, mainly lactose, sugar alcohols (mannitol, sorbitol), salts such as dicalcium phosphate or sodium chloride, and cellulose derivatives such as microcrystalline cellulose. They can also act as a cohesive component that aids in the formation of a compact solid, disintegrating agents, flavor modifiers, or stabilizers. Current trends in pharmaceutical excipients are oriented towards modifying their properties so that they can display multiple roles in the formulation, thus allowing compositions with fewer ingredients.

b. **Binders:** These are materials that bind powder particles together into agglomerates, i.e., granules, and also by additional adhesion of the granules to each other during tablet compression. They can be used as dry powders in dry granulation processes or as solutions in wet granulation. Granulation processes will be discussed in later parts of this section. Examples of dry binders are cellulose derivatives, while wet binders that form sticky, viscous solutions are gelatin, starch, sucrose, glucose, polyvinylpyrrolidone, and gums arabic and tragacanth.

C . Disintegrants:

Also called disintegrants, these are components that facilitate tablet breakage upon exposure to an aqueous environment. They have a capillary structure that leads to water absorption and swelling, thus causing the tablet to break into pieces. Commonly used disintegrants are cellulose derivatives (carboxymethyl cellulose, microcrystalline cellulose), starch, and cross-linked polyvinylpyrrolidone.

d. Lubricants

These are components that prevent powders and granules from sticking to the metal surfaces of the tableting machine, particularly the punches and dies, and they reduce friction between the particles during compression, ensuring better transmission of the compression force into the granule mass. Thus, they enable the formation of an intact tablet and facilitate tablet ejection from the compression chamber. Lubricants are added to the granules just before compression.

The most commonly used lubricant is magnesium stearate. Stearic acid, talc, and sodium stearyl fumarate also aid lubrication. All lubricants have gliding properties to a lesser extent, and vice versa.

e. Various Adjuvants

e.1 Buffer Substances

These are intended to protect the active ingredient against pH variations, against the hydrolyzing or inactivating action of digestive fluids, or to reduce their irritating effect on the mucous membranes. These include: calcium carbonate, calcium or sodium citrates, and glycine.

e.2 Colorants

These are added dry or in solution for aesthetics (to improve the appearance of the tablet) and identification (to avoid confusion between two dosages of the same active ingredient).

e.3 Flavorings and Sweeteners

These are used to mask an unpleasant taste or flavor.

e.4 Absorbents and Adsorbents

These are used to retain certain volatile ingredients.

3. Study of the physicochemical parameters of tablets:

The physicochemical analysis of tablets assesses their quality and compliance by measuring parameters such as hardness, friability, disintegration, dissolution, and weight variation. These tests ensure that the tablet has the appropriate mechanical strength, disintegration, and release of the active ingredient for optimal efficacy and safety. Further analyses include particle size, moisture content, and chemical composition.

Physical and mechanical parameters

• Hardness:

Measures the tablet's resistance to rupture under applied pressure.

• Friability:

Evaluates the tablet's tendency to crumble during handling or shipping.

• Weight Variation:

Verifies whether the weight of each tablet conforms to the expected average weight.

• Disintegration:

Determines the time it takes for the tablet to disintegrate in a liquid medium.

• Dissolution:

Measures the rate and extent of release of the active ingredient into a solvent.

Powder and Tablet Parameters

• Particle Size: Analyzes the powder's particle size, which influences flow and compressibility.

• Bulk Density: Indicates how well the powder is packed before compression.

• Moisture Content: Measures the amount of water present, which can affect stability and mechanical properties.

Other Analyses

• Chemical and Compositional Analyses:

Verify the uniformity of the active ingredient content and the presence of impurities or degradation products.

• Stability tests:

Evaluate the drug's resistance to environmental stresses (light, temperature, humidity) to ensure its shelf life.

4. Tablet Manufacturing:

The manufacturing of a pharmaceutical tablet is a complex process that involves several steps. Here are the main ones:

1. Weighing and Dosing of Raw Materials:

- Equipment used: Precision balances, weighing stations (such as those integrated into the I-Box+ isolator for handling CMR products).
- Description: The active raw materials and excipients are precisely weighed according to the formula specifications.

2. Granulation:

- Types: Wet or dry granulation.
- Equipment used: Granulators, mixers.
- Description: This step improves the flow and compression properties of the powders. Wet granulation involves the addition of a binding liquid, followed by drying, while dry granulation does not require a liquid.

3. Mixing:

- Equipment used: High-shear mixers, drum mixers.
- Description: The resulting granules are mixed to ensure a homogeneous distribution of the active ingredients and excipients.

4. Compression:
- Equipment used: Tableting machines.
- Description: The mixed granules or powders are compressed into tablets. Tableting machines apply pressure to form tablets of uniform size and shape.

5. Coating (if necessary):
- Types: Film-forming coating, enteric coating.
- Equipment used: Coating machines.
- Description: This step is used to mask the taste, protect the active ingredient from the external environment, or control drug release. The tablets are coated with a thin layer of polymers or other substances.
6. Quality Control:
- Tests Performed: Hardness, Friability, Dosage Uniformity, and Dissolution.
- Equipment Used: Dissolution Testing Devices, Tablet Hardness Testers.
- Description: Each batch of tablets undergoes a series of tests to ensure they meet pharmaceutical specifications.

7. Packaging:
- Types: Blister packs, bottles.
- Equipment Used: Automatic packaging machines.
- Description: The tablets are packaged for distribution. The packaging protects the tablets from moisture, light, and contaminants.

8. Labeling and Packaging:
- Equipment Used: Labeling machines, packaging machines.
- Description: The packages are labeled with the relevant information (drug name, dosage, expiration date) and prepared for shipment.

9. Storage and Distribution:
- Description: The finished products are stored under controlled conditions until distribution.
Each manufacturing step is critical and must be carried out in accordance with Good Manufacturing Practices (GMP) to ensure the safety, efficacy, and quality of pharmaceutical tablets.

5. Tablet Testing

Tablets manufactured for the pharmaceutical market must undergo rigorous analytical testing to ensure product integrity. Guidelines for these analytical tests are published in the European Pharmacopoeia, an annually published reference that also contains reference standards for dosage forms, pharmaceutical products (drug monographs), and excipients. There are several types of analytical tests, as presented below:

a. Appearance

This is a visual inspection that allows for the detection and recording of abnormalities (cleavage, decapsulation, roughness, etc.) as well as the general appearance of the tablets (gloss, color consistency, etc.).

b. Hardness

The hardness test is important in quality control and formulation development procedures.
This analysis evaluates the force required to crush a tablet by applying a diametrical force. The manner in which the tablet breaks should also be noted, as rolling and capping can indicate problems in the manufacturing process.

c. Friability

The tablets are placed in a device in which they are subjected to collisions and drops for a specified period of time. The tablets are weighed before and after this treatment.
Friability is expressed as the percentage loss of mass relative to the initial mass.
For a compact to be compliant, the pharmacopoeia requires friability of less than 1%.

d. Dose Uniformity

According to the European Pharmacopoeia, the individual active ingredient content of the units comprising the sample is determined, verifying that it is within the established limits compared to the average content of the sample.

e. Mass Uniformity

The test is performed on ten to twenty tablets. They are weighed individually and the average mass and standard deviation are determined. The European Pharmacopoeia provides the specification based on the mass of the tablet.

f. Dissolution Test

This is more representative of the future availability of the active ingredient to the body.
The most common apparatus is a U-shaped tube filled with water at 37°C. At the bottom of this tube is a tablet topped by a rotating paddle that rotates at a slow but sufficient speed (250 rpm, for example). A dissolution apparatus is shown for capsules; the paddle is replaced by a rotating basket. It is estimated that at least 60% of the active ingredient is dissolved in less than 30 minutes. In some cases, water can be replaced by a liquid simulating digestive fluids (pH, enzymes).

g. Disintegration or Disintegration Time

This test, described in the European Pharmacopoeia, is intended to determine the ability of tablets to disintegrate, in a liquid medium, within a prescribed time. The European Pharmacopoeia describes a standardized apparatus for this test. The device consists of cylindrical tubes fitted with a metal grid immersed in a 1-liter cylindrical vessel.
For the tests, one tablet is placed in each tube and the entire assembly is tested in a liquid at 36-38°C, which can be distilled water, 0.1 M hydrochloric acid, or a pH 6.8 phosphate buffer solution, depending on the tablet being tested.

Disintegration is considered achieved when:
- There is no residue left on the grid, or
- If a residue remains, it consists solely of a soft mass with no palpable core and is not impregnated.

The disintegration time should not exceed
15 minutes.

6. Other types of tablets:

a. Membrane-coated tablet:

This is a tablet covered with a coating (film coating), which can be a thin layer of plastic or polymer. This coating serves several purposes: improving presentation, masking an unpleasant taste, facilitating swallowing by increasing lubrication, protecting the active ingredients from external influences such as moisture, and modulating drug release (e.g., enteric coating for dissolution in the intestine rather than the stomach).

- Purposes of the coating
• Facilitating swallowing: The smooth surface of the coating makes the tablet easier to swallow.
• Masking tastes and odors: The coating covers an unpleasant taste or odor from the active ingredient.
• Protecting the drug: It protects the active ingredients from degradation caused by air, light, or moisture. • Modulate release:
o Delayed release: An enteric coating protects the tablet from stomach acid so it dissolves in the intestine.
Extended-release: Other types of film coatings allow the active ingredient to be released gradually over a longer period of time, reducing the need for frequent dosing.
• Improve appearance: It gives the tablet a more aesthetically pleasing and uniform appearance.

b. Modified-release tablet:

Some dosage forms are specially formulated to release active ingredients slowly or in small, repeated doses, usually over a period of 12 hours or more. This dosage form is called modified, controlled, continuous, or extended-release.
b.1- Accelerated-release tablet: An accelerated-release tablet disintegrates quickly, often in the mouth, so that the active ingredient is absorbed quickly. There are two main types: effervescent tablets (which dissolve in a glass of water) and orodispersible tablets (which break down in the mouth upon contact with saliva).
b.1.1. Effervescent Tablets
• Fast-acting: They release the active ingredient quickly after dissolving in a glass of water.

• Directions: They must be dissolved in half a glass of water before drinking.
b.1.2. Orodispersible Tablets
• Fast-acting: They disintegrate very quickly in the mouth upon contact with saliva, without the need for water.
• Directions: Place the tablet under the tongue, where it dissolves quickly so that the active ingredient passes directly into the bloodstream.
• Handling: It is important to handle them with dry hands and store them in their original packaging, as they are often sensitive to moisture.
b.2-Delayed-release tablet:
A delayed-release tablet is a pharmaceutical form designed to release its active ingredient at a specific time, often after a delay, typically in the intestine. This technology protects active ingredients that irritate the stomach or are degraded by gastric acid. Unlike an extended-release tablet, which ensures slow and continuous release, a delayed-release tablet releases the medication once it has passed the stomach.
How it works
• Special coating: The tablet is coated with a film that is resistant to the acidic environment of the stomach.
• Intestinal release: This film dissolves in the more alkaline environment of the intestine, releasing the medication.
• Benefits: This protects the stomach lining from irritation, preserves the medication from acidic breakdown, and allows for targeted action in the intestine if needed.
b.3-Extended-release tablet:
An extended-release tablet (or LP/ER/XR) releases its active ingredient slowly and continuously into the body over a longer period of time. This allows for reduced dosing frequency, ensures a more consistent drug concentration, and improves treatment compliance and tolerance. It is crucial not to bite or chew these tablets, as this could alter their release mechanism.
Key Benefits
• Long-acting: The medication works for a longer period of time, reducing the number of daily doses.
• More stable concentration: Helps maintain a more consistent level of the medication in the body, which can improve effectiveness and reduce fluctuations.
• Better tolerability: The gradual release can help reduce some side effects.
Improved adherence: Fewer doses per day make it easier to follow treatment.
Important precautions
• Do not crush or chew: These tablets are specially designed for slow release. Crushing or chewing them would destroy this mechanism.
• Follow the instructions: It is essential to read the package leaflet or ask your doctor or pharmacist, as instructions may vary depending on the medication. For example, some can be taken with or without food, while others may require a dose adjustment in cases of kidney or liver impairment.
• Do not share: These medications are prescribed for specific needs and should never be shared.

7. Conclusion

In the pharmaceutical industry, most tablets are manufactured using one of three methods: direct compression, wet granulation, and dry granulation.
Of these three methods, wet granulation is the most widely used. However, the choice of method depends on the characteristics of the active ingredient and other excipients used in the process.
Granulation is one of the most important unit operations in the production of pharmaceutical dosage forms. These specialized granulation techniques have led to the production of granules with good flow properties, compressibility, a good release profile, improved stability, and reduced production costs.